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LETTERS TO THE EDITOR

Comments on "Cellular Therapies for Treatment of Radiation Injury after a Mass Casualty Incident" (Radiat Res 2017; 188:242-45)

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It was with a great interest that we have read the articles ''Cellular Therapies for Treatment of Radiation Injuries after a Mass Casualty Incident''[1] by C. Rios, J. R. Jourdain and A. L. DiCarlo and Workshop Report ''Cellular Therapies for Treatment of Radiation Injury: Report from a NIH/NIAID and IRSN Workshop'' by DiCarlo *et al*. Indeed, there is, from our point of view too, a great need in animal model development to overcome the current limits in the use of mesenchymal stromal/stem cells (MSCs) to mitigate radiation damages at the level of numerous tissues, especially cutaneous and muscular. One of them is the low efficacy, if any depending of the targeted tissue, of unmatched MSCs from banking that could be the first line of defense in a (military) mass casualty scenario (Percy military hospital and Centre de Transfusion sanguine des Armées). As an example, our group was unable to observe any efficacy after iterative injections of allogeneic adipocyte derived stem cells in a minipig model, which strongly contrasted with the efficacy of autologous cells (*1*). In this model, iterative injections of autologous cells were required to enhance cutaneo-muscular wound healing with the limitation that no early injection schedule was tested. Studies are currently being performed to explore derived strategies such as culture cell media use and micro vesicles injection but it is yet unclear whether these approaches would present any therapeutic efficacy *in vivo* in the context of radiation-induced injuries. In addition, it is likely that preferentially localized treatments could be achieved in this way. Albeit expensive such strategies need to be tested in large animal models such as minipig. Regarding the specific use of MSCs to cope with irradiated/war casualties the point of feasibility (or not) of allogeneic cell use, with matching constraint or after manipulation, remains the crucial one before embarking in any large approach. Finally, we would like to indicate the need to clarify the confusing point in the paper indicating that the minipig studies cited have been conducted in the ''French Armed Forces Biomedical Research Institute'' facility by a military team thanks to a grant from the Délégation Générale de l'Armement'' under our supervision–all colleagues who are not from the prestigious IRSN.

REFERENCE

1. Riccobono D, Agay D, Scherthan H, Forcheron F, Vivier M, Ballester B, et al. Application of adipocyte-derived stem cells in treatment of cutaneous radiation syndrome. Health Phys 2012;103:120–6.

Editor'note. DiCarlo *et al*. wish to thank the authors for pointing out an error in the original publication, as well as apologize for the inaccuracy and appreciate the clarification.

The LSS Cohort of Atomic Bomb Survivors and LNT. Comments on "Solid Cancer Incidence among the Life Span Study of Atomic Bomb Survivors: 1958–2009" (Radiat Res 2017; 187:513–37) and "Reply to the Comments by Mortazavi and Doss" (Radiat Res 2017; 188:369–71)

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We read with interest the articles by Grant *et al*. (*1*) and critique by Mortazavi and Doss (*2*) with reply by the original authors (*3*). In their original article, on p. 523, under the subheading *''Examination of Threshold,''* Grant *et al*. assert (emphases added):

''The evidence of a threshold dose below which there was no dose response was examined using linear-quadratic threshold models for males and linear threshold models for females. There was no evidence of a threshold for females (estimated threshold dose of 0.08 Gy). *This was not significantly different from 0* ($P = 0.18$) and the upper 95% confidence bound was 0.2 Gy. For males, the best estimate for a threshold dose was 0.75 Gy. *Similarly, this was not significantly different from 0* ($P = 0.49$).''

Further, near the end of the ''Summary and Discussion'' section (*1*), the authors say (emphasis added):

''These uncertainties taken together with inconsistencies with prior LSS analyses and the findings from other studies *precludes* [*sic*] *definitive conclusions that might confidently guide the development of modified radiation protection policies at this time*.''

Grant *et al*. arbitrarily and implicitly enlist the absence of a nonzero threshold (or equivalently a threshold of zero dose) as their effective null hypothesis, which they find the data do not permit them to ''reject'', i.e., their estimates for thresholds derived from the LSS data cannot be distinguished statistically from zero. Then they go on to commit a common logical fallacy. They, in effect, ''*accept*'' this null, absence of a (nonzero) threshold, as the valid scientific model.

However, failure to reject a null is not the same as confirming it to be valid, since failure to reject may only result from ''insufficient data'' rather than from the null's validity. In the case of LSS, the data are indeed insufficient due to large uncertainties, as exhibited, first, from the fact that the best-estimate dose threshold, 0.75 Gy, as cited above for males, is not statistically–significantly different from zero. Second, a Monte Carlo simulation by Socol and Dobrzyński (*4*) confirms that the statistical power of the LSS cohort is insufficient to discriminate between the linear no-threshold (LNT) model and a threshold hypothesis. LNT is the most commonly accepted non-threshold model.

Given the authors' major new result, new for RERF publications, that the male dose response was nonlinear, they deserve credit for introducing into consideration a nonlinear model (linear quadratic) with the possibility of a nonzero threshold (linear-quadratic threshold).

We agree with Grant *et al*. that LSS analyses preclude definitive conclusions that can guide *any* radiation protection policies in the low-dose region, including the present policies based on LNT. However, given the current domination of regulatory policies by the LNT paradigm and their effective acceptance of (rather than failure to reject) their arbitrarily assigned zero-threshold null, Grant *et al*. lend their imprimatur to retention of current policies. LNT has *never* been validly shown to be scientific truth, as opposed to a mathematically simple default extrapolation from high doses. Their inability to exclude it (based on insufficient data) should not, as they assert, prevent definitive conclusions to guide policies, based on the following. Present policies completely *ignore or dismiss without refutation an entire literature* demonstrating the reality of thresholds and adaptive hormetic effects (*5, 6*) and need to be modified, as they bear an extremely high price tag in both economic and human terms (*7–10*).

And in their response to the critique by Mortazavi and Doss (*2*), Grant *et al*. (*3*) say [emphasis added]:

''We endeavor to approach our analyses *without preconceived notions of the nature of the dose response* and stand by our conclusions''.

Thus, they deny any bias toward the absence of a nonzero threshold. However, as pointed out above, their effective default acceptance of a zero-threshold model as the basis of policy betrays a *significant* bias.

NCRP President John Boice, admitting that the LNT model is an assumption that has not been and cannot be scientifically validated in the low-dose range due to the signal-to-noise problem and that other dose-response relationships cannot be excluded, nevertheless, in concert with the current judgment by national and international scientific committees, asserted in 2015 that ''no alternative dose-response relationship *appears more plausible* than the LNT model on the basis of present scientific knowledge'' [emphasis added] (*11*).

The conclusions of Grant *et al*. are perfectly compatible with Boice's subjective view, but given the uncertainties of the LSS data, their analyses are also at least as consistent with a *non*zero-threshold model (linear threshold or linear-quadratic threshold) as with any zero-threshold model.

REFERENCES

1. Grant EJ, Brenner A, Sugiyama H, et al. Solid cancer incidence among the Life Span Study of atomic bomb survivors: 1958–2009. Radiat Res 2017;187: 513–537.
2. Mortazavi SMJ, Doss M. Comments on ''Solid Cancer Incidence among the Life Span Study of Atomic Bomb Survivors: 1958–2009'' (Radiat Res 2017; 187:513–537). Radiat Res 2017; 188. DOI: 10.1667/RR4811.1.
3. Grant EJ, Brenner A, Sugiyama H, et al. Reply to the comments by Mortazavi and Doss on ''Solid Cancer Incidence among the Life Span Study of Atomic Bomb Survivors: 1958–2009'' (Radiat Res 2017; 187:513–537). Radiat Res 2017; 188. DOI: 10.1667/RR4811.1.
4. Socol Y, Dobrzyński L. Atomic bomb survivors life-span study: insufficient statistical power to select radiation carcinogeneis model. Dose Response 2015 May 4;13(1). doi: 10.2203/dose-response.14-034.Socol.
5. Aurengo A, Averbeck D, Bonnin A, et al. Dose effect relationships and estimation of the carcinogenic effects of low doses of ionizing radiation. Paris: Académie des Sciences - Académie Nationale de Médecine; March 2005.
6. Tubiana MF, Feinendegen LE, Yang C, Kaminski JM. The linear no-threshold relationship is inconsistent with radiation biologic and experimental data. Radiology 2009; 251:13–22.
7. Socol Y, Dobrzyński L, Doss M, et al. Commentary: ethical issues of current health-protection policies on low-dose ionizing radiation, Dose Response 2014;12:342–348.
8. Siegel JA, Welsh JS. Does imaging technology cause cancer? Debunking the linear no-threshold model of radiation carcinogenesis. Technol Cancer Res Treat 2016; 15: 249–256.
9. Sacks B, Meyerson G, Siegel JA. Epidemiology without biology: false paradigms, unfounded assumptions, and specious statistics in radiation science (with commentaries by Inge Schmitz- Feuerhake and Christopher Busby and a reply by the authors). Biol Theory 2016; 11: 69–101.
10. Siegel JA, Pennington CW, Sacks B. Subjecting radiological imaging to the linear no-threshold hypothesis: a non sequitur of non-trivial proportion. J Nucl Med 2017; 58: 1–6.
11. The Boice Report #40: LNT 101. Health Phys News 2015;XLIII (9):25–26.